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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,999	07/18/2003	Ronit Yahalomi	1662/611054	3044

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EXAMINER	
CHANG, CELIA C	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,999	YAHALOMI ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *5-41 and 43-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,42,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-4, and 42 in the reply filed on Feb. 2, 2006 is acknowledged. The traversal is on the ground that "if the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits even though they include claims to independent or distinct inventions". This is not found persuasive because the two criteria of restriction as the basis of applicants' traversal are met. For (A) the polymorphs, were they independent and distinct products, are made and sold separately and process of making one polymorph can not product another polymorph i.e. a different product; (B) the **is** a serious burden in searching each and every polymorph since the physical data and parameters of producing such polymorph must be separately search and examined. Applicants provided no reason or basis of what was "overlapping". In addition, applicant did not submit evidence or identify such evidence of record showing the inventions to be obvious variants or clearly admit on the record that this is the case, does applicants' allegation of overlapping making an admission that each polymorph is an obvious variant of another? In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 42 and 61-62 reading on claim 1 are prosecuted. Claims 5-41, 43-60 and the remaining scope of 61-62 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claims 1-4, 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is very confusing as to what is the scope of the claims. Please note that one category of patentable invention is a "product". A novel or unobvious chemical product is identified first by its "chemical nature, i.e. elemental content and their ratios. It is a well known in the pharmaceutical art that drugs are known to have polymorphic forms (see US pharmacopia #23, national formulary #18,1995 of record). It was well known "fact" that "many pharmaceutical

solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Thus *in the strictest sense, polymorphs are different crystalline forms of the **same pure substance** in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 2). Therefore, for a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavalability, easy of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p.185).

In the field of crystal chemistry (Evans, p.284-285), it is well recognized that solvates/hydrates which containing coordinating solvent molecule/water for which when the solvent/ water is removed will loss its crystalline structure are "isolated site solvates/hydrates" which can be identifiable by a different molecular formula. Other solvates/hydrates known as clathrates or channel solvates/hydrates etc. which are identical crystalline products with solvents/water being trapped in the interstices among the crystalline frame works and such inclusion is strictly purely by mechanical constraints. The product is the same crystalline molecules with *impurities* mechanically trapped in its interstices (Evans p.396).

The instant claim 1, claims a nateglinide characterized by XRPD while the dependent claim 42 claims the same compound being a solvate of xylene. This is very confusing. It is unclear as to what is the product of the claims is it a compound with its innate physical property/ or is it a group of compounds some are solvates, with a specific crystalline structure.

If the scope of the claims are drawn to crystalline nateglinide which has the physical property of XRPD, due to inclusion of certain solvents, then, the following 102(b) rejection applies. If the scope of the claims are drawn to nateglinide xylene solvate, then, the following 112 first paragraph rejection applies.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 61-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. Acta Pham. Sinica; Chinese J. Pham. Ana. (both cited on 1449) supplemented with US Pharmacopia #23. Please note that the two Li references disclosed X-ray diffraction patterns very similar to the instant claims. US pharmacopia provided evidence that the innate nature of many pharmaceutical crystals is that there existed polymorphic forms which contains inclusion material. Such inclusion may result in small changes in X-rays which may not be truly another crystal.

In the field of crystal chemistry (Evans, p.284-285), it is well recognized that solvates/hydrates which containing coordinating solvent molecule/water for which when the solvent/ water is removed will loss its crystalline structure are "isolated site solvates/hydrates" which can be identifiable by a different molecular formula. Other solvates/hydrates known as clathrates or channel solvates/hydrates etc. which are identical crystalline products with solvents/water being trapped in the interstices among the crystalline frame works and such inclusion is strictly purely by mechanical constraints. The product is the same crystalline molecules with *impurities* mechanically trapped in its interstices (Evans p.396).

In absence of objective evidence, the instant claims are drawn to innate nature of the crystal wherein the same crystalline product as the prior art, but the physical properties differ only within the range of value being measured i.e. melting point $\pm$ 2%, X-ray peaks $\pm$ 5% etc.

In addition, artisan in the field has clearly understood that *"in strict sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p.2).

Given the innate nature of the crystals that they are readily transformed into the thermodynamically stable form as disclosed on page 13, the innate nature that upon pharmaceutical formulation the same identical thermodynamically stable form pharmaceutical composition of the prior art is found (see innate nature, US pharmcopia). In addition, at physiological environment wherein the drug is being used for treating lowering blood sugar, the same "drug" of the prior art was found, i.e. anticipation. Please note that there is no evidence that the drug functions on its form instead of depending on the chemical nature in an aqueous environment wherein all forms are dissolved as liquid or amorphous form.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 42, 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. Acta Pham. Sinica; Chinese J. Pham. Ana. (both cited on 1449) in view of Brittain, Evans and US Pharmacopia #23.

The instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug. There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction pattern, melting point etc. Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268. Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that the new form provided a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, easy of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see Brittain p.2, 185).

The prior art disclosed the product nateglinide with various crystalline with the prima facie recognition that in pharmaceutical art that multiple forms may occur in drugs which will give different X-ray pattern but not all of them are polymorphs (see US pharmacopia). In

addition, X-ray diffraction pattern are identification of "crystals" i.e. physical forms, it does not provide information on the chemical nature. As it is well recognized in the art, inclusion crystals or clathrates are "identical" crystalline form with mechanically trapped impurities. Such trapped impurity, although may change the X-ray diffraction pattern (US pharmacopia or Evans) are not different crystals.

Given the innate nature of the crystals that they are readily transformed into the thermodynamically stable form as disclosed on page 13, the innate nature that upon pharmaceutical formulation the same identical thermodynamically stable form pharmaceutical composition of the prior art is found (see innate nature, US pharmcopia). In addition, at physiological environment wherein the drug is being used for treating lowering blood sugar, the same "drug" of the prior art was found, i.e. anticipation. Please note that there is no evidence that the drug functions on its form instead of depending on the chemical nature in an aqueous environment wherein all forms are dissolved as liquid or amorphous form. Even there existed some residue of the new form, the dosage, and efficacy are prima facie obvious variation within the prior art such as using a lesser or more pure product.

5. Claims 1-4, 42, 61-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description as well as the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention; or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A survey of the specification indicated that no process or how to make form A was found. Further, it was clearly described on page 13 that "the various crystalline forms are related to each other in that *drying of one form may result in a transformation to another form*...". Therefore, in the specification, there lacks sufficient support that form A was a stable product. A transient intermediate may provide measurements by physical means but to entitle to a claim of a product, an obtainable product with beneficial utility is the requirement.

It is known in the polymorphic art that while polymorphs can be prepared, the maintenance of such meta- or pseudo-stable form in an obtainable fashion does not come automatically but have to be demonstrated (see Kirk-othmer encyclopedia e-book p. 3). The specification provided no guidance as to the maintenance of the X-ray diffraction in a stable product with an advantage in terms of stability, formulation, solubility, bioavailability, easy of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see Brittain p.2, 185).

Further, it is conventional knowledge in the art a particular pseudopolymorphs such as solvates can only be obtained with highly specific condition which provides stability of maintenance the particular pseudopolymorph (Kirk-othmer p. 3). The specification provided no process of making form A with sufficient specificity in condition that is required for the preparation of the particular solvated form. Given the innate nature of the crystals for nateglinide on page 13, X-ray diffraction measurements with variations in transient crystal transformation are insufficient support in identification of polymorphs.

Given the innate nature of the claimed product (see p. 13 specification) and in absence of any objective disclosure that the particular form A can be made into a pharmaceutical composition with measurable parameter that the "form A" actually is maintained, the specification provided no description as to how such a composition or such a form can be made or used in therapeutic process.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Mar. 23, 2006

Celia Chang
Primary Examiner
Art Unit 1625